

Claim 2 recites "[a] method of attaching hydrophilic species to hydrophilic macromolecules immobilized on a hydrophobic surface, said method comprising the steps: (i) providing a hydrophobic surface, (ii) immobilizing hydrophilic macromolecules on the hydrophobic surface, (iii) exposing the hydrophilic macromolecules immobilized on the hydrophobic surface to hydrophilic species, whereby the hydrophilic species are attached to the hydrophilic macromolecules" (emphasis added). Ford and Klein do not disclose or suggest such a method.

The Office Action relies on Ford for its alleged disclosure of providing a hydrophilic substrate, immobilizing hydrophilic nucleic acids on the substrate, and metallizing the immobilized nucleic acids with a hydrophilic species. *See* Office Action, pages 2 to 3. The Office Action relies on Klein for its alleged disclosure of immobilizing a hydrophilic nucleic acid on a hydrophobic substrate. *See* Office Action, page 3. It is undisputed that neither Ford nor Klein discloses or suggests the combination of immobilizing hydrophilic macromolecules on a hydrophobic surface and exposing the macromolecules to a hydrophilic species.

The Office Action asserts that it would have been obvious to combine the teachings of Ford and Klein to obtain a method "that is easy to employ and results in high yield." *See* Office Action, page 3. As is well-settled, a *prima facie* case of obviousness based on a proposed combination of references (e.g., replacing the hydrophilic substrate of Ford with the hydrophobic substrate of Klein) will only stand if one of ordinary skill would have had a reasonable expectation of success upon making the modification. *See, e.g.*, MPEP §2143.02 (citing *In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986)). One of ordinary skill in the art would have had no reason to expect that the method of Ford would function employing a hydrophobic substrate as disclosed in Klein.

It is well known that many hydrophilic species (e.g., water soluble globular proteins or antibodies), notwithstanding their hydrophilicity, adsorb irreversibly to hydrophobic

surfaces upon contact. This property creates difficulties for those of ordinary skill in the art, for example, when performing protein purification in the presence of plastic lab ware. When an aqueous protein solution contacts hydrophobic surfaces, such as plastic test tubes or dialysis tubing, protein material is irreversibly lost. This phenomenon of non-specific adsorption is described, for example, in U.S. Patent No. 5,516,703 to Caldwell et al. (which is cited in the Office Action and discussed below). *See, e.g.*, column 1, lines 44 to 59. One of ordinary skill in the art would not expect to be able to control the deposit of hydrophilic species on a hydrophobic substrate. Rather, one of ordinary skill in the art would expect that the hydrophilic species would bind randomly to the hydrophobic substrate.

In view of the foregoing, one of ordinary skill in the art would not expect success if attempting to expose hydrophilic macromolecules immobilized on a hydrophobic substrate to a hydrophilic species, such as metal nanoparticles, to bind the hydrophilic species to the hydrophilic macromolecules. Rather, one of ordinary skill in the art would expect non-specific reactions between the hydrophilic species and both the hydrophobic substrate and the hydrophilic macromolecules. This non-specific reactivity would have dissuaded one of ordinary skill in the art from attempting to replace the hydrophilic substrate of Ford with the hydrophobic substrate of Klein.

Moreover, Applicants submit that Klein taken either as a whole or in view of its specific teachings does not fairly suggest employing hydrophobic substrates in broader contexts, as proposed in the Office Action. For example, Klein discloses that "patterned DNA on a substrate can serve as templates for wires and for two and three-dimensional nanoscale devices." *See Klein*, page 2396, left-hand column, lines 25 to 27. However, this teaching is plainly in the context of hydrophilic substrates, such as glass or silane-treated substrates. *See Klein*, page 2396, left-hand column, lines 14 to 18. In view of this teaching, one of ordinary skill in the art would understand that hydrophilic substrates could potentially

serve as templates for wires, etc. However, hydrophobic substrates would remain, even in the view of a skilled artisan versed with the teachings of Klein, plagued by the non-specific adsorption issues discussed above.

Applicants surprisingly discovered that exposure of a hydrophilic species (e.g., an aqueous solution of gold nanoparticles) to a hydrophobic substrate (e.g., polystyrene) on which hydrophilic macromolecules are immobilized provides a desirable result. Namely, the hydrophilic species binds specifically (i.e., almost exclusively) to the hydrophilic molecule, and not the hydrophobic substrate. *See, e.g.*, present specification, pages 10 to 11. That is, the hydrophilic species does not bind non-specifically to the hydrophobic substrate as would have been expected in view of past experience relating to the binding of hydrophilic species to hydrophobic substrates.

As neither Ford nor Klein discloses or suggests the combination of immobilizing hydrophilic macromolecules on a hydrophobic surface and exposing the macromolecules to a hydrophilic species, and one of ordinary skill in the art would not expect success upon combining Ford and Klein as proposed in the Office Action, the combination of Ford and Klein would not have rendered obvious claim 2.

As explained, claim 2 would not have been rendered obvious by Ford and Klein. Claims 3-11, 14-18 and 20 depend from claim 2 and, thus, also would not have been rendered obvious by Ford and Klein. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

B. Ford, Klein and Tajima

The Office Action rejects claims 12 and 13 under 35 U.S.C. §103(a) over Ford in view of Klein and U.S. Patent No. 4,649,071 to Tajima et al. ("Tajima"). Applicants respectfully traverse the rejection.

Claim 2 is set forth above. For the reasons discussed above, Ford and Klein do not disclose or suggest the method of claim 2. Tajima does not remedy the deficiencies of Ford and Klein. Tajima is cited for its alleged disclosure of the water contact angle of polystyrene. *See* Office Action, page 4. However, Tajima, like Ford and Klein fails to disclose or suggest the combination of immobilizing hydrophilic macromolecules on a hydrophobic surface and exposing the macromolecules to a hydrophilic species. Accordingly, the combination of Ford, Klein and Tajima fails to render obvious claim 2.

As explained, claim 2 would not have been rendered obvious by Ford, Klein and Tajima. Claims 12 and 13 depend from claim 2 and, thus, also would not have been rendered obvious by Ford, Klein and Tajima. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

C. Ford, Klein and Berning

The Office Action rejects claim 19 under 35 U.S.C. §103(a) over Ford in view of Klein and Berning et al., "¹⁹⁸Au Labeled Hydroxymethyl Phosphines as Models for Potential Therapeutic Pharmaceuticals," Nuclear Medicine and Biology, 25: 577-583 (1998) ("Berning"). Applicants respectfully traverse the rejection.

Claim 2 is set forth above. For the reasons discussed above, Ford and Klein do not disclose or suggest the method of claim 2. Berning does not remedy the deficiencies of Ford and Klein. Berning is cited for its alleged disclosure of tris(hydroxymethyl)phosphine-gold nanoparticles. *See* Office Action, page 4. However, Berning, like Ford and Klein fails to disclose or suggest the combination of immobilizing hydrophilic macromolecules on a hydrophobic surface and exposing the macromolecules to a hydrophilic species. Accordingly, the combination of Ford, Klein and Berning fails to render obvious claim 2.

Applicants further note that Berning fails to disclose or suggest tris(hydroxymethyl) phosphine-gold nanoparticles, as recited in claim 19. Berning discloses only a gold complex in which a single gold atom in an ionic (+1) state is complexed with tris(hydroxymethyl) phosphine. One of ordinary skill in the art would not understand this complex to be a nanoparticle. Rather, one of ordinary skill in the art would expect a nanoparticle to be much larger, e.g., including 50-150 gold atoms in a neutral (0) state. Berning does not disclose or suggest such a nanoparticle.

As explained, claim 2 would not have been rendered obvious by Ford, Klein and Berning. Claim 19 depends from claim 2 and, thus, also would not have been rendered obvious by Ford, Klein and Berning. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

D. Ford and Shueller

The Office Action rejects claims 2, 3 and 14-18 under 35 U.S.C. §103(a) over Ford in view of U.S. Patent Application Publication No. US 2002/0050220 to Schueller et al. ("Schueller"). Applicants respectfully traverse the rejection.

Claim 2 is set forth above. Ford and Schueller fail to disclose or suggest such a method.

The Office Action relies on Ford for its alleged disclosure of providing a hydrophilic substrate, immobilizing hydrophilic nucleic acids on the substrate, and metallizing the immobilized nucleic acids with a hydrophilic species. *See* Office Action, page 5. The Office Action relies on Schueller for its alleged disclosure of immobilizing a hydrophilic nucleic acid on a hydrophobic substrate. *See* Office Action, page 3. It is undisputed that neither Ford nor Schueller discloses or suggests the combination of immobilizing hydrophilic macromolecules on a hydrophobic surface and exposing the macromolecules to a hydrophilic species.

The Office Action asserts that it would have been obvious to combine the teachings of Ford and Schueller to obtain "an improved method for stamping materials on a substrate." See Office Action, page 5. Applicants submit that one of ordinary skill in the art would not have expected that the method of Ford would function employing a hydrophobic substrate as disclosed in Schueller, for the reasons discussed above with respect to Ford and Klein.

Applicant further note that Schueller's disclosure of both hydrophobic substrates (*see* paragraph [0068]) and hydrophilic substrates (*see* paragraph [0065]), can hardly be called a suggestion that hydrophobic substrates be employed. Rather, understanding the difficulties relating to non-specific adsorption to hydrophobic substrates discussed above, one of ordinary skill in the art would remain, even after reviewing the teachings of Schueller, discouraged from attempting to employ a hydrophobic substrate in the method of Ford.

As neither Ford nor Schueller discloses or suggests the combination of immobilizing hydrophilic macromolecules on a hydrophobic surface and exposing the macromolecules to a hydrophilic species, and one of ordinary skill in the art would not have expected success upon combining Ford and Schueller as proposed in the Office Action, the combination of Ford and Schueller would not have rendered obvious claim 2.

As explained, claim 2 would not have been rendered obvious by Ford and Schueller. Claims 3 and 14-18 depend from claim 2 and, thus, also would not have been rendered obvious by Ford and Schueller. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

E. Ford, Schueller and Tajima

The Office Action rejects claims 12 and 13 under 35 U.S.C. §103(a) over Ford in view of Schueller and Tajima. Applicants respectfully traverse the rejection.

Claim 2 is set forth above. For the reasons discussed above, Ford and Schueller do not disclose or suggest the method of claim 2. Tajima does not remedy the deficiencies of Ford and Schueller. Tajima is cited for its alleged disclosure of the water contact angle of polystyrene. *See* Office Action, page 4. However, Tajima, like Ford and Schueller fails to disclose or suggest the combination of immobilizing hydrophilic macromolecules on a hydrophobic surface and exposing the macromolecules to a hydrophilic species.

Accordingly, the combination of Ford, Schueller and Tajima fails to render obvious claim 2.

As explained, claim 2 would not have been rendered obvious by Ford, Schueller and Tajima. Claims 12 and 13 depend from claim 2 and, thus, also would not have been rendered obvious by Ford, Schueller and Tajima. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

F. Ford, Schueller and Berning

The Office Action rejects claim 19 under 35 U.S.C. §103(a) over Ford in view of Schueller and Berning. Applicants respectfully traverse the rejection.

Claim 2 is set forth above. For the reasons discussed above, Ford and Schueller do not disclose or suggest the method of claim 2. Berning does not remedy the deficiencies of Ford and Schueller. Berning is cited for its alleged disclosure of tris(hydroxymethyl) phosphine-gold nanoparticles. *See* Office Action, page 4. However, Berning, like Ford and Schueller fails to disclose or suggest the combination of immobilizing hydrophilic macromolecules on a hydrophobic surface and exposing the macromolecules to a hydrophilic species. Accordingly, the combination of Ford, Schueller and Berning fails to render obvious claim 2.

Also, as discussed above, Berning fails to disclose or suggest tris(hydroxymethyl) phosphine-gold nanoparticles, as recited in claim 19.

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As explained, claim 2 would not have been rendered obvious by Ford, Schueller and Berning. Claim 19 depends from claim 2 and, thus, also would not have been rendered obvious by Ford, Schueller and Berning. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Double Patenting

The Office Action rejects claims 2-6, 11, 15 and 17-19 under the judicially created doctrine of obviousness-type double patenting over claims 1-4, 14-16 and 20 of U.S. Patent Application No. 09/990,049 in view of U.S. Patent No. 5,516,703 to Caldwell et al. Applicants respectfully request that this provisional rejection be held in abeyance until the 049 application issues as a patent or the present application is otherwise indicated to be in condition for allowance.

Conclusion

For the foregoing reasons, Applicants submit that claims 2-20 are in condition for allowance. Prompt reconsideration and allowance are respectfully requested.

Respectfully submitted,

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